Exhibit A

FORBES EXPERT REPORT

John M. Graham, Jr., M.D., ScD

CREDENTIALS

1) I am a board-certified pediatrician and medical geneticist, with over 35 years of training and experience in clinical genetics, dysmorphology, teratology, developmental disabilities, communicative disorders, and public health aspects of birth defects.

2) I completed a pediatric internship and residency, as well as fellowships in developmental disabilities and dysmorphology. During my dysmorphology training, I did original research on the teratogenic effects of alcohol, fetal constraint, and maternal hyperthermia. This work was published in peer-reviewed journals, and since that time, I have continued to publish on teratogenic syndromes, genetic syndromes, and other factors that cause birth defects.

3) I was a steering committee member and co-founder of the David W. Smith Workshop on Malformations and Morphogenesis, which is a nationally recognized conference on the causes of birth defects, which has been held annually since 1980, and I continue to attend and advise organizers of this meeting. I hold a Professor of Pediatrics Emeritus Lifetime Appointment at UCLA School of Medicine, where I am on the UCLA Intercampus Medical Genetics Training Program Executive Committee. Beginning in 1988, I served as Director of Clinical Genetics and Dysmorphology at Cedars Sinai Medical Center (CSMC) in Los Angeles. I recently retired from this full-time position, but I continue to treat patients at CSMC and Harbor-UCLA Medical Center, and I teach genetics, teratology, embryology, and dysmorphology to medical students at UCLA and

CSMC, as well as to residents and fellows in medical genetics, neonatology, and maternal fetal medicine. Between 1981 and 1988, I held similar positions at Dartmouth Medical School in New Hampshire.

4) I am an academic clinical geneticist, who previously saw about 500 outpatients per year and covered the inpatient medical genetics consultation service for a major part of the year (resulting in another 30-40 patients per year). My experience covers a wide variety of clinical problems, including craniofacial disorders, growth disorders, birth defects, intellectual disability, genetic conditions, and teratogenic disorders. Over the past 35 years, I have provided diagnostic evaluations for over 10,000 fetuses, infants, and children manifesting various birth defects, developmental disabilities, malformation syndromes, genetic diseases, and teratogenic disorders. I have seen additional patients in interdisciplinary clinics where I helped to provide care for craniofacial patients, spina bifida patients, and/or patients with developmental disabilities.

5) I currently serve on the Section of Genetics and Birth Defects and the Section of Child Development for the American Academy of Pediatrics. I have served on the Editorial Boards for the following journals: *Teratology*, *Birth Defects Research*, *American Journal of Medical Genetics*, *Congenital Anomalies* (Japan), *Annales de Génétique* (France), *European Journal of Medical Genetics*, *Global Pediatric Health,* and *Clinical Pediatrics*. I am a past president of the Teratology Society, where I also served on the Council for many years. I have participated in Craniofacial Clinics, Spina Bifida Clinics, and Developmental Disabilities Clinics where I provided care for numerous children with birth defects in a multidisciplinary setting. I am a past president

of the Society for Craniofacial Genetics.

6) I have authored over 240 publications in peer-reviewed journals, as well as over 100 reviews, book chapters and one book. I have been an investigator on numerous grants from a variety of organizations and governmental agencies dealing with intellectual disability and birth defects, and I have served as a medical advisor and lecturer for numerous support groups for families of children with various genetic syndromes.

7) I have been a longstanding and active member of numerous professional organizations and academic societies concerned with the health of children and with the causes and prevention of birth defects, including the American Society of Human Genetics, European Society of Human Genetics, American College of Medical Genetics, American Board of Medical Genetics, American Academy of Pediatrics, Society for Pediatric Research, American Pediatric Society, Western Society for Pediatric Research, Teratology Society, American Cleft Palate-Craniofacial Association, and the Society for Craniofacial Genetics.

8) My credentials, training, publications, and experience are more fully set forth in my *Curriculum Vitae*, attached as Appendix A.

9) A listing of previous legal matters where I have given deposition and/or court testimony during the past 4 years is attached as Appendix B. My fee for consulting is $500.00 per hour.

10) The medical records, depositions, and literature that I reviewed and considered in this case are listed in Appendix C. I also considered the references cited in

this report, as well as textbooks, guidelines, and general literature reviews that have been part of my years of experience and training.

BACKGROUND

11) I am familiar with and have reviewed the scientific data addressing the human reproductive and developmental effects of valproic acid (Depakote or VPA).

12) I was asked to discuss the general science of teratology and address the cause of B[redacted] F[redacted]'s spina bifida. In conducting this analysis, I employed the same methodology as I regularly employ in my clinical practice and research. Expressed to a reasonable degree of medical and scientific certainty, my opinions are based on available publications, the materials that I considered for this case (Appendix C), the references set forth below, and my previous education, training, research, and experience. If new information becomes available, I reserve the right to amend or supplement my opinions.

The Science of Birth Defects: Background Rates and Causes

13) Every infant born in the U.S. has at least a 3%-5% risk of being born with a structural defect, such as a malformation (2-3%) or deformation (2-3%), and an even higher risk (approximately 10%) of being born with internal anomalies or functional deficits, which might not become apparent until later in life (Graham and Sanchez-Lara, 2015; Jones, Jones and Del Campo, 2013). The specific cause of most isolated congenital anomalies is unknown in the vast majority of cases. In at least 95% of spina bifida cases, the cause is unknown.

14) Almost all birth defects, and spina bifida in particular, are multi-factorial and include a combination of both genetic and environmental (or teratogenic) influences. (Holmes et al. 2012; see also www.marchofdimes.org, www.cdc.gov;

www.spinabifidaassociation.org, www.mayoclinic.com, www.ghr.nlm.nih.gov). There are a number of ways in which an alteration or error can occur in genetic information, leading to structural malformations in the developing embryo. Genomics is the study of complex sets of genes, their interactions and their effect on biology, while genes are the functional units of inheritance that are passed from parents to their offspring. Although it is presently impossible to identify the genetic cause for most isolated birth defects, research in this area has progressed significantly in recent years and can be expected to continue to advance in the future. It is believed that genetic factors account for the vast majority of human malformations, and that research will continue to elucidate the specific genomic mechanisms for most defects.

15) Environmental factors contributing to birth defects include all the non-genetic factors affecting embryonic environment and leading to congenital malformations. The most common environmental causes of birth defects are maternal disease states, such as obesity and diabetes. Chemical or drug exposures of any kind are believed to account for only a small fraction of birth defects, with the proportion attributable to medicinal compounds being even smaller. Medicines are estimated to account for 1% or less of all birth defects.

Genetic Risk Factors for Congenital Malformations

16) It is believed that most spina bifida cases likely have a genetic basis. As we have learned more about the human genome and developed new diagnostic tests over the last decade, the proportion of birth defects attributed to genetic causes has increased. Most multifactorial defects, such as congenital heart defects, NTDs, club feet or clefts of the lip and/or palate, are associated with a large number of genetic and environmental

influences, but other than the routine use of chromosomal microarrays to look for submicroscopic genomic alterations that might result in malformations, specific gene panels for common isolated malformations are not available for clinical use in the evaluation of children born with specific multifactorial defects. As stated above, in at least 95% (i.e., the vast majority) of children born with spina bifida, the exact cause remains unknown.

17) There are numerous types of genetic alterations, such as mutations (changes to the DNA sequence of genes) or genomic defects (*e.g.,* chromosomal alterations or epigenetic changes). Genetic alterations leading to malformations can be inherited, or they can occur spontaneously due to random mutations of DNA. Genetically mediated malformations have never been shown to result from exposure to environmental agents, even those agents which are capable of causing damage to genetic material in individual cells, such as heavy doses of ionizing radiation or cancer chemotherapy.

18) Birth defects can occur as isolated defects, or as part of a pattern of multiple birth defects. With some isolated birth defects, malformations in related structures can occur as part of a malformation sequence (*e.g.*, cleft palate can occur as an isolated malformation, or it can occur secondary to a primary failure in closure of the lip; hydrocephalus, bladder/bowel incompetence or clubfeet can occur secondary to the impact of spina bifida on the spinal cord). When multiple birth defects affecting various organs and systems appear together and are seen in different individuals in different families in a recurrent pattern or combination, they are generally accepted to have a common underlying cause and termed a birth defect syndrome.

19) Alteration in the genetic material of any germ cell in the body can cause a genetic disease or genetic birth defect syndrome. Genetic alterations generally occur in either the sperm or the egg, or both, prior to or at the time of conception. It is also possible that the genetic material of the sperm and egg could be "normal," but shortly after conception (within hours, or a few days), a mutation occurs during subsequent cell replication, resulting in mosaicism. Genetic disorders can also be inherited from the affected individual's normal parent(s). Among the over 20,000 pairs of genes in the human genome, it is important to realize that one member of each pair is derived from each parent. Because genes work in pairs, a person can have a working gene and a defective gene, and still be a normal person (gene carrier).

20) Genetic factors heavily influence the risk for malformations, including spina bifida, and all of these variables must be taken into account when evaluating the risk for malformations associated with a specific drug exposure during pregnancy. Mutations in the *VANGL1* and *VANGL2* genes have been found in individuals with familial and sporadic NTDs. Mutations in *FUZZY* have also been described in patients with NTDs. Variation in the *DACT1* gene have been associated with NTDs. Folate-sensitive NTDs have been associated with variations in a number of genes involved in folate and homocysteine metabolism, including *MTHFR*, methionine synthase (*MTR*), methionine synthase reductase (*MTRR*), and methylenetetrahydrofolate dehydrogenase-1 (*MTHFD1*). Women with elevated plasma homocysteine, low folate, or low vitamin B12 (cobalamin) are at increased risk of having a child with a NTD, and folic acid given before and during the first 4 weeks of pregnancy can significantly reduce the risk of NTDs and other folate-responsive birth defects, such as cleft lip and palate. It should be

noted that the 677C-T mutation in the *MTHFR* gene has been associated with elevated homocysteine levels, low folate status, increased risk for premature cardiovascular disease , thrombosis, strokes, coronary artery disease, and hypertension in adults, as well as NTDs, cleft lip and cleft palate, depression and migraines, and all of these risks are ameliorated to some extent by taking supplemental folic acid (OMIM Entry #607093; *MTHFR*; Liew and Gupta, 2015).

21) There is no evidence that environmental exposures can lead to the types of genetic errors that cause congenital malformations. Even studies of factors known to alter genetic material (such as radiation) have not been shown to increase the risk for birth defects in exposed mothers or infants. For example, after atom bombs were exploded over Japan, a careful study of the exposed population over the next 4-5 generations demonstrated no increase in birth defects or genetic diseases (in exposed fetuses) caused by new mutations, despite significant exposure to radiation, a highly potent mutagen. Similarly, studies of the offspring of cancer patients who received radiation or chemotherapy treatment have failed to show any increase in the rate of malformations, and cancer chemotherapy treatments are also often mutagenic. Based on our current scientific knowledge, mutations leading to birth defects are not induced by external environmental exposures, but rather they just happen in the normal course of cell division. The only factor demonstrated to increase the risk of genetic alterations that lead to congenital malformations, and also neurodevelopmental alterations, is advanced paternal age in the male. (Crow, 2006; Kong, et al., 2012).

22) Common birth defects occurring in an otherwise normal child are usually thought to be multifactorial (*i.e.*, potentially attributable to a combination of genetic and

environmental effects) when they occur without other evidence to suggest an underlying syndrome with a genetic or teratogenic etiology.

Environmental Risk Factors for Congenital Malformations

23) In addition to genetic and chromosomal abnormalities, maternal disease states and environmental exposures have been associated with an increased risk for birth defects. Environmental causes of birth defects have been the subject of scientific investigations for well over 50 years. Environmental causes of human malformations (defined as any external influence to embryo-fetal development, *i.e.*, not genetic) are thought to account for a low percentage of all malformations (Brent, 2004). The prevailing view among scientists and medical professionals is that most environmentally induced malformations are related to relatively common maternal disease states, such as infection, diabetes, obesity and/or alcoholism. It is estimated that only approximately 1% of all human malformations are related to drug exposures, chemicals, or radiation (Brent, 2004), making them relatively rare causes for malformations in comparison with all other potential causes.

24) There are common maternal conditions that specifically increase the risk of spina bifida. As discussed more fully below, VPA is associated with an increased risk of spina bifida. Maternal diabetes is associated with an increased risk of spina bifida (Greene 1999; Shaw, et al., 2003; Anderson, et al., 2005; Correa, et al., 2008; Correa, et al., 2012; Garne, et al., 2012; Agopian, et al., 2013), as is maternal obesity (BMI > 30), overall OR of 11 studies 1.70, CI 1.34-2.15 (Rasmussen, et al., 2008), which has been confimed by 3 subsequent studies (Waller, et al., 2007; Stothard et al, 2009; Marengo, et al., 2013; Block, et al., 2013). Severe obesity (BMI > 40) is associated with an even

higher risk for spina bifida (OR 3.11, CI 1.5-5.46) in a meta-analysis of 12 previous studies by Rasmussen et al. (2008). Obesity together with gestational diabetes also increases the risk for spina bifida (Anderson, et al., 2005). Maternal hyperthermia and fever also increase the risk of spina bifida (Chambers 1998, Suarez 2004, Moretti 2004, Wang 2014). This includes prolonged use in a hot tub or sauna. Maternal stress is associated with an increased risk of spina bifida (Carmichael, et al., 2007; Carmichael, et al., 2014), and periconceptional maternal use of opioid analgesics also increases the risk of spina bifida. (Broussard, et al., 2011; Yazdy et al. 2013).

Folic Acid and Spina Bifida

25) Periconceptional folic acid supplementation is also a major factor in reducing both the occurrence and recurrence of spina bifida (Collins, et al., 2011; DeMarco, et al., 2011; Correa, et al., 2012; Kennedy and Koren, 2012; Parker, et al., 2013). Inadequate intake of folic acid or lack of folic acid supplementation has also been associated with an increased risk for spina bifida. (Obican et al., 2010, DeMarco et al., 2011, Correa, et al., 2012, Kennedy and Koren, 2012, Parker, et al., 2013). It is not established that lack of folic acid or a folate deficiency is of no consequence when a person is taking valproic acid (Morrell 2002, AED Pregnancy Registry Winter 2007 Newsletter, 2009 Practice Parameter Update, Kennedy & Koren 2012). Folate deficiency is still a potential cause of spina bifida, regardless of VPA use, especially when other factors such as severe obesity reduce the efficacy of folate supplementation. As recommended by Kennedy & Koren (2012), “Women who are at high risk of having babies with neural tube defects and who would benefit from higher doses of folic acid include those with certain folate-enzyme genotypes, previous pregnancies with neural

tube defects, diabetes, malabsorption disorders, or obesity, or those who take antifolate medications or smoke. Such women should take 5 mg/d of folic acid for the 2 months before conception and during the first trimester."

VPA

26) It is generally accepted that first-trimester exposure to VPA increases the risk of spina bifida. (Arpino, et al., 2000; Wide, et al., 2004; Morrow, et al., 2006). Hernandez-Diaz, et al. (2012) reported a 1.2% overall absolute risk for spina bifida while Jentink, et al. (2010) reported a 0.6% overall absolute risk for spina bifida, with an OR 12.7, CI 7.7-20.7 compared with no AED, and an OR 5.7, CI 2.6-12.3 compared with other AEDs. Werler et al. (2011) reported an association between VPA and neural tube defects with an OR 9.7 (CI 3.4-27.5). However, there is no substantial evidence that 750mg of Depakote increases the risk of spina bifida significantly, if at all. (Omtzigt, et al. 1992, Samren, et al. 1999, Canger, et al. 1999, Vajda et al. 2013). For example, the aforementioned studies found no cases of spina bifida in babies exposed to 750mg per day of Depakote, or less.

Dysmorphic Features Associated with VPA

27) Because most human teratogens are associated with a recognizable pattern of altered morphogenesis, early case reports and clinical series looked for and reported specific facial features in association with other malformations in infants born to mothers on VPA, (DiLiberti, et al., 1984; Winter et al., 1987; Ardinger, et al., 1988; Sharony, et al., 1993; Kozma, et al., 2001; Malm et al., 2002; Clayton-Smith et al., 1995; Kini et al., 2006). The facial features, sometimes termed fetal valproate syndrome, include a narrow bifrontal diameter, high forehead, telecanthus, wide and low nasal bridge with short nose,

long philtrum, midface hypoplasia, relatively small mouth, and micrognathia. Related limb defects include triphalangeal thumbs, preaxial ray, tibial deficiency defects, and polydactyly (Sharony, et al. 1993; Alessandri, et al., 2010; Jentink, et al., 2010). Dysmorphic features have also been associated with other AEDs. (Jones, Kl, et al. 1989; Kini et al., 2006, Jentink et al., 2010).

Beth and B[redacted] F[redacted]

28) I have reviewed the medical records relating to Beth and B[redacted] F[redacted] B[redacted] F[redacted] (DOB[redacted]) was his mother's 5th pregnancy. B[redacted]'s parents were each 33 years old at the time of his birth. The pregnancy was apparently unplanned, and conception occurred around 1/1/05.

29) Prior to B[redacted]'s birth, his parents had 2 children (without any birth defects) followed by two miscarriages, and his mother became progressively more obese during the time period spanning these pregnancies. Medical records reflect measured heights of 5'7.5" on 8/11/04 and 5'7.6" on 6/4/02, so I have used a height of 5'7.5" to calculate Mrs. Forbes' BMI. Mrs. Forbes went from a BMI of 33.5 (weight 217) on 5/30/1996 during her first pregnancy to a BMI of 43.2 (weight 279.8) at the beginning of her pregnancy with B[redacted] on 1/31/05.

30) On 1/31/2005, Mrs. Forbes reported to her doctors that she was taking Depakote, Geodon, and Wellbutrin XL 300. Pharmacy records from December 2004 and January 2005 show that Mrs. Forbes was prescribed the following doses of those medicines: Depakote ER 750 mg/day, Geodon 80 mg/day, and Wellbutrin XL 300 mg/day. On 2/4/2005, Dr. Moore instructed Mrs. Forbes to discontinue Depakote. Mrs. Forbes testified that she was taking Vitamin E and folic acid at the time of her conception

with B[redacted]. However, the first pharmacy or medical record of any prenatal vitamins was on 3/30/05. Mrs. Forbes denied alcohol consumption, smoking, and street drugs during her pregnancy.

31) During her pregnancy, Mrs. Forbes had an elevated 1-hour glucose challenge test on 7/14/05 (193 mg/dl), followed by a normal 3-hour glucose tolerance test on 7/19/05, a normal thyroid screen on 3/11/05, and a negative thrombophilia evaluation 2/4/05. No HbA1C levels were done, which is a long-term measure of serum glucose to test for diabetes. Moreover, the medical records reflect that all of Mrs. Forbes's live-born children were large for gestational age, suggesting that she had abnormal glucose homeostasis and may have had gestational diabetes during her pregnancy with B[redacted]. On a 6/17/13 visit to her internist, Mrs. Forbes had elevated random glucose (230 mg/dL), glucosuria, ketosuria, obesity (BMI 52.5), hypertension (138/82), and dyslipidemia. Her hemoglobin A1C was 8.7, which is consistent with diabetes, and an average glucose level of 203.0 mg/dL. Her total cholesterol was elevated at 210 mg/dL (normal 40-199), and her triglycerides were also elevated at 199 mg/dL (normal 0-150). Mrs. Forbes testified that subsequent to that visit she was diagnosed with diabetes and takes Metaformin.

32) A January 27, 1998 record from Dr. Snidle states that Mrs. Forbes has a paternal cousin with spina bifida. Other family history indicated that Mrs. Forbes has a brother with obesity, diabetes and heart issues. Mrs. Forbes's mother also has diabetes and had congestive heart failure, and her paternal grandfather had diabetes and coronary artery disease. Her half-brother was thought to have fragile X syndrome, but Mrs. Forbes was tested on 4/21/05 and found not to be a carrier. CF Carrier testing was negative on 8/5/04.

33) On 4/21/05, fetal lumbo-sacral meningomyelocele was diagnosed at 17 5/7 weeks and confirmed at 25.6 weeks on 6/15/05, along with left clubfoot. Chiari malformation was noted 7/13/05 at 29.6 weeks, and B[redacted] was noted to be large for gestational age (> 90th centile). Mrs. Forbes had persistently elevated diastolic blood pressures during the pregnancy, so B[redacted] was delivered by cesarean section at 37.4 weeks on 9/7/05. His 3-vessel cord placenta was very large (610 gms; >90th centile), and he was large for gestational age with birth weight 4155 gms (97th centile), length 50 cm (50-90th centile), and OFC 34 cm (50-90th centile).

34) B[redacted] was born with Apgar scores of 8 and 8 at 1 and 5 minutes. He had a 5 X 8 cm lower lumbar myelomeningocele with bloody CSF drainage due to a perforated sac. He demonstrated some upper leg movement, but none below the knees. His OFC was 35 cm on day 2. His spinal defect was repaired on 9/8/05 by neurosurgeon Dr. Jeff Leonard, who also inserted a right frontal VP shunt for hydrocephalus with Chiari malformation on 9/14/05 at St Louis Children's Hospital. On 9/15/05, orthopedics evaluated B[redacted] for bilateral clubfeet and indicated his heel cords were not tight. Orthopedics recommended serial casting and followed him, noting on 5/16/06 "excellent correction of clubfeet, 30 degrees of ankle dorsiflexion, wearing a night brace 12-14 hours, negative Ortolani and Barlow." Urology followed him for a neurogenic bladder.

Summary and Opinions

35) In my opinion, to a reasonable degree of medical certainty, there is insufficient evidence to conclude that 750 mg/day of Depakote was a substantial factor in causing B[redacted]'s spina bifida or that B[redacted] was born with spina bifida as a direct result of his mother's ingestion of Depakote. Mrs. Forbes was on a low-dose of Depakote (750

mg). As discussed above, there is insufficient medical evidence to establish that a low dose of 750 mg/day of Depakote increases the risk of having a child with spina bifida to any extent, and certainly not to a substantial extent. Thus, it cannot be concluded that the 750 mg/day dose of Depakote taken by Mrs. Forbes was a substantial factor, or any factor, in causing B[redacted]'s spina bifida. In addition, an examination of family photographs reveals that B[redacted] does not have any of the specific facial or limb features that have been associated with Depakote exposure *in utero*. There are also no medical records stating that B[redacted] has any unusual or dysmorphic facial features or radial ray defects.

36) There are also other reasons why Depakote, to a reasonable degree of medical certainty, was not a substantial factor in causing B[redacted]'s spina bifida. As I have discussed, spina bifida is almost always multifactorial and genetic susceptibilities are always a factor. The vast majority of spina bifida cases are considered to be idiopathic and likely to have a genetic basis. B[redacted] has had no genetic evaluations to determine the basis of his congenital anomalies.

37) Moreover, while medical science has not yet discovered many of the genetic issues that lead to spina bifida, geneticists know that there must be a genetic explanation for the fact that 98-99% of women who use Depakote do not have a child with spina bifida and 1-2% do. There is something genetic that makes this 1-2% different. The best explanation for these patients is that they metabolize folic acid differently and thus have a folic acid deficiency. Folic acid is necessary for the cell division of cells that is critical to a developing embryo. If not enough cells divide and replicate, the neural tube will not close. That is why any factor that leads to folic acid deficiency (for example, poor metabolization for genetic reasons, lack of folic acid

supplementation and/or morbid obesity) can contribute to spina bifida.

38) Also, general risk data cannot be used in a vacuum to establish or attribute causation in an individual case after the injury has occurred (Agopian et al. 2013). Medical science is rarely able to determine the causes of spina bifida in a particular individual. In each individual case, all of the relevant and individual facts and factors need to be analyzed in order to properly assess the issue of causation. As explained, I have analyzed those facts and factors in this case.

39) In addition to genetics, B[redacted]'s spina bifida could have resulted from his mother's morbid obesity. B[redacted]'s mother was morbidly obese prior to her pregnancy, which as stated above, increased her risk of having a child with spina bifida threefold. (Rasmussen 2008). Increasing degrees of obesity are associated with increased risks for major congenital malformations and folic acid dependent birth defects like spina bifida and cleft lip and palate. (Green et al., 2012, Rasmussen et al., 2008). Larger mothers have lower levels of folic acid and require supplemental doses of folic acid prior to and during early pregnancy to achieve adequate levels of folic acid to promote normal embryonic development. Br[redacted]'s mother lacked adequate folic acid supplementation. While Mrs. Forbes testified that she was taking folic acid and a vitamin pill at the time she became pregnant, there are no medical or pharmacy records stating that Mrs. Forbes was taking the recommended amount of 5 mg/d of folic acid for the 2 months before conception and during the first trimester (Kennedy and Koren, 2012). This is especially important because of Mrs. Forbes' morbid obesity. A woman with Mrs. Forbes's BMI needed the birth defects prevention amount of folic acid supplementation (4-5 mg/day). I do not believe that Mrs. Forbes would have had enough folic acid through a regular diet

and a 0.4 mg/day folic acid pill to decrease her obesity-related risk of spina bifida.

40) Both of Mrs. Forbes's two prior live-born children were also large for gestational age, suggesting abnormal glucose homeostasis. Mrs. Forbes was also diagnosed with diabetes in the summer of 2013. There is a significant family history of diabetes. Therefore, in light of Mrs. Forbes's morbid obesity, prior abnormal glucose homeostasis, and current diabetes, Mrs. Forbes likely had gestational diabetes or pre-diabetes early in her pregnancy with B[redacted] which contributed to B[redacted]'s spina bifida. (Anderson 2005).

41) As referenced above, a 1/27/98 record from Dr. Snidle states that Mrs. Forbes has a paternal cousin with spina bifida. A family history of spina bifida increased Mrs. Forbes's risk of having a child with spina bifida. (www.spinabifidaassociation.org).

42) There are also other factors that can cause spina bifida that cannot be ruled out here, such as a fever or elevated body temperature during pregnancy, or mental stress. (Suarez 2004, Moretti 2004, Wang 2013, Carmichael 2014).

43) Also, the vast majority of mothers who take Depakote during pregnancy do not have a child born with spina bifida.

44) It also cannot be concluded that B[redacted] Forbes would not have been born with spina bifida if his mother had not been taking Depakote. Other alternative mood stabilizers such as Lithium, Lamotrigine and Tegretol are associated with an increased risk of birth defects. Therefore, it cannot be said to a reasonable degree of medical certainty that there would not have been a birth defect if Mrs. Forbes had been taking some different medication to treat her psychiatric condition.

45) Finally, I have reviewed the opinions of plaintiffs' proffered expert Dr.

Land. To the extent that B[redacted] Forbes has strabismus, I disagree that it can be concluded to a reasonable degree of medical certainty that B[redacted]'s strabismus resulted from his spina bifida. I am aware of literature which has found an association between spina bifida and strabismus. A higher prevalence of strabismus in individuals with spina bifida myelomeningocele has previously been attributed to hydrocephalus, but hydrocephalus can be caused by other conditions than spina bifida. Anderson et al. (2012) also found that in children with spina bifida and strabismus, lower birth weight and younger gestational age at birth were related to the occurrence of strabismus, and children who had at least one shunt revision were more likely to have strabismus. Anderson also found that spinal lesion level was significantly related to strabismus with increased likelihood of strabismus for spinal lesions closer to the brain. Since B[redacted] was born at term with a large birth weight and a low spinal lesion, and has not had a shunt revision, it cannot be concluded to a reasonable degree of medical certainty that if B[redacted] has strabismus today, that it was caused by his spina bifida or hydrocephalyus. Moreover, strabismus is most commonly found independent from spina bifida. The great majority of patients with spina bifida do not have strabismus.

46) I also disagree with Dr. Land that B[redacted]'s unilateral high frequency hearing loss was a result of his spina bifida and shunted hydrocephalus. There is insufficient evidence to attribute B[redacted]'s right-sided hearing loss to his shunted hydrocephalus. There are many causes of hearing loss including genetics and viral infections, and shunted hydrocephalus is not considered to be a primary cause of hearing loss. Thus, I disagree that there is sufficient evidence to conclude to a reasonable degree of medical certainty that B[redacted]'s high frequency hearing loss resulted from his spina bifida and hydrocephalus.

Date: June 26, 2015

JOHN M. GRAHAM, JR., M.D., Sc.D.